Slap It On!
Topical Medications in Palliative Care

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I currently have, or I have had in the past two years, an affiliation with/or financial interests in a business corporation, or I receive remuneration, royalties, or research grants from a business corporation.

- Valeant Pharmaceuticals Canada
  Consultant
- Wyeth Pharmaceuticals
  Consultant and Advisory Board member
- GW Pharmaceutical
  Clinical Trial Investigator and Advisory Board member
Learning Objectives

Discuss the options of using the topical or transdermal route of drug administration
List indications for use of topical medications
Review the science and the evidence behind topical medications
Discuss initial clinical use and results
## Delivery Routes for Medications

<table>
<thead>
<tr>
<th><strong>Standard</strong></th>
<th><strong>Alternative</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Sublingual</td>
</tr>
<tr>
<td>Intravenous</td>
<td>transmucosal</td>
</tr>
<tr>
<td>Inhalation (nebulized)</td>
<td>mouthwashes</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Intranasal</td>
</tr>
<tr>
<td></td>
<td>Transdermal (topical)</td>
</tr>
<tr>
<td></td>
<td>Rectal</td>
</tr>
<tr>
<td></td>
<td>Vaginal</td>
</tr>
<tr>
<td></td>
<td>Intraosseous</td>
</tr>
</tbody>
</table>
Reasons for Topical Route

Oral route not desirable
  Mucositis
  Inability to swallow
  Nausea/vomiting
  Gastric/ bowel obstruction
  Poor taste of product/taste alterations

More localized action

Easily accessible

Systemic adverse effects
Topical Route: Advantages

Avoids the GI tract and hepatic first-pass metabolism
Delivers to a specific site
Controls absorption rate
Provides constant dosing → depot effect with anhydrous gels
Reduces systemic side effects

Heir G et al. *IJPC* 2004; 8:337-343
Topical Route: Advantages

Improves compliance
Allows ↑ concentration of Rx at site of application
Plasma concentrations of <10% compared to oral route

Heir G et al. *IJPC* 2004; 8:337-343
Topical Route: Drawbacks

Variations in the stratum corneum barrier
  Delivery dosing may require adjustment
  Rate of absorption may vary
Rash most common AE
Cumbersome when using larger areas
Patient compliance
Cost

Heir G et al. IJPC 2004; 8:337-343
Topical Route

Ophthalmology
   topical meds commonplace

Dermatology
   lotions, ointments, gels, etc.

Internal medicine
   blood pressure, pain control, infections, etc.

Gynecology
   hormone patches, antibiotic creams
Topical Route

Transdermal Route

- Fentanyl, scopolamine, estrogen, nitrate patches
- Transdermal gels (Pennsaid®)
- Ointments (Flamazine®)
- Lotions/creams (steroids or antibiotics)
- Sunblock (local blockade, ?absorption)
Topical Opioids

Classically, opioids active on CNS receptors
mu (μ) kappa (κ) delta (δ) receptors
Now found on:
- peripheral neurons
- immune cells
- inflamed tissue
- respiratory tissue
- GI tract
Why Topical Opioids?

Opioid receptors on peripheral neurons & dorsal root ganglia
Inflammation $\uparrow$ receptors, activation
Macrophages produce opioid peptides
Peptides $\downarrow$ neuron excitability
Exogenous opioids $\downarrow$ pain, inflammation
Activated receptors respond to topical Rx

Stein C. *NEJM* 1995; 332:1685-1690
Peripheral Sensory Neuron

Stein C. NEJM 1995; 332:1685-1690
Symptom Prevalence: Wounds

Pain ~50%

Other symptoms ?

Lindholm et al. J Wound Care 1999;8:5-10
Clinical Concerns: Malignant Wounds

<table>
<thead>
<tr>
<th>Concern</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>21%</td>
</tr>
<tr>
<td>Emotional stress</td>
<td>18%</td>
</tr>
<tr>
<td>Odor</td>
<td>16%</td>
</tr>
<tr>
<td>Exudate</td>
<td>11%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>10%</td>
</tr>
<tr>
<td>Functional compromise</td>
<td>7%</td>
</tr>
<tr>
<td>Social concerns</td>
<td>6%</td>
</tr>
<tr>
<td>Edema</td>
<td>5%</td>
</tr>
<tr>
<td>Complications</td>
<td>5%</td>
</tr>
</tbody>
</table>

Schulz V et al. *JPSM* 2002;24 572-77
Causes of Wound Pain

- **Operative**: (cutting of tissue or prolonged manipulation normally requiring anaesthetic, e.g., debridement, major burns dressings)

- **Procedural**: (routine/basic interventions, e.g., dressing removal, wound cleansing, dressing application)

- **Incident**: (movement-related activities, e.g., friction, dressing slippage, coughing)

- **Psychosocial Factors**: (e.g., age, gender, culture, education, mental state – anxiety, depression, fear, loss/grief)

- **Environmental Factors**: (e.g., timing of procedure, setting – level of noise/positioning of patient, resources)

- **Background**: (persistent underlying pain due to wound aetiology, local wound factors, e.g., ischaemia, infection)

WUWHS, 2004
Chronic Wound Inflammation

Alters nerves:
  excitability, expression of transmitters and receptors

Alters immune system:
  blood flow, vascular permeability, immune cells, chemicals

Alters spinal processing of pain
Why Topical Opioids?

Inflammation ↑ peripheral receptors, activation
Macrophages, lymphocytes produce opioid peptides (in turn, ↓ neuron excitability)
Exogenous opioids ↓ pain, inflammation
Activated receptors respond to topical Rx

Stein C. NEJM 1995; 332:1685-1690
Topical Opioids: Benefits

Small doses, little systemic absorption
High local concentration
Less side effects

↓ constipation, N/V, sedation
decreased risk of toxicity
no known drug interactions

Ease of use → better compliance

Topical Opioids

**Case series**

Diamorphine 10 mg in IntraSite® gel
- relief in 3 pts
- duration 1 wk to 2 mo

Morphine 0.1% in IntraSite® (1 mg/ml)
- 8/9 reported relief
- duration few days to > 1 yr

Back IN & Findlay I. *JPSM* 1995;10:493
Topical Opioids

Zylicz et al

Series of papers, 7 patients
Morphine gel (0.08%-0.5%)
Pain rapidly ↓, lasted up to 8 hrs
Duration of up to 2 mo
Minimal side effects

Krajnik M, Zylicz Z. Pall Med 1997; 11:325-26
Krajnik M, Zylicz Z. Prog Pall Care 1997; 5:101-06
Topical Opioids

*Diamorphine in IntraSite® gel*
RCT, double-blind, 13 pts, II/III decubitus ulcers
Placebo x 3/diamorphine (0.1% w:w) x 3; switch
Pain assess before, 1 h & 12 h after application
Significant relief in tx group (n=6) vs placebo
A/E: pruritis, skin irritation
No significant systemic effects seen

Flock P. JPSM 2003; 25:547-554
Topical Opioids

**Morphine in IntraSite® gel**
- RCT, double-blind, 5 pts, painful sacral ulcers
- Morphine 10 mg/ml in 8 g IntraSite®
- Placebo x 3/morphine x 3 or opposite (2 d w/o)
- Pain twice daily using VAS
- Significant relief in tx group vs placebo
- A/E: pruritis, burning, skin discomfort

Zeppetella G et al. *JPSM* 2003; 25:555-8
Topical Opioids: Bioavailability

Open label study, X-over, 6 hospice in pts
Topical vs SC morphine
Serial blood levels post therapy
Morphine, M6G, M3G in SC pts
Only detected 1 topical pt (largest ulcer)
No AEs in topical pts, drowsiness in SC
Topical opioids act locally, no systemic absorption

Topical Opioids: Bioavailability

RCT, X-over, 5 volunteers
Topical morphine \( (10 \text{ mg/ml}) \) in PLO 1 ml + SC placebo
Topical placebo + morphine \( (3\text{ mg/ml}) \) 1 ml SC
Serial blood levels (16) post therapy
Morphine detected in SC samples only
Topical opioids not systemically absorbed

Topical Opioids

*Methadone in Stomahesive® powder*

Case series, 4 pts, 3 non-malignant wounds
Topical morphine gel not effective

Methadone 100mg / 10g Stomahesive®
Dry powder worked in open, exudative wounds

Absorption measured via serum levels

Effective in 3 cases, esp. with open wounds

Topical Analgesics

Science?  Rationale?
Structure of Skin

Largest organ of the human body
Skin is composed of 3 primary layers
  - Epidermis → 5 strata
  - Dermis
  - Hypodermis (Subcutaneous adipose layer)
Structure of Skin

Epidermis

Stratum Corneum (Horny layer)

- Final product of epidermal cell differentiation
- “Bricks & mortar”
- Regulates transdermal water loss & prevents external access
- Thickness varied
Structure of Skin

- **Epidermis**
  - **Stratum Corneum (Horny layer)**
    - Final product of epidermal cell differentiation
    - "Bricks & mortar" for regulating transdermal water loss and preventing external access
    - Thickness varied
Structure of Skin

Dermis

Major component of skin
Network of connective tissue
Hydrophilic = challenging for lipophillic drugs
Regulation of body temperature
Blood supply maintains [gradient]
? “Shunt routes” for early permeation
3 main appendages

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Structure of Skin

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Permeation Pathways
(Stratum Corneum)

Transappendageal transport
Transcellular route
Intercellular pathway

Relative contributions of these pathways to the gross flux will depend on the physicochemical properties of the permeant

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
ENLARGED: stratum corneum

- Transcellular
- Intercellular
- Transappendageal

Epidermis
- Deep sensory receptor
- Dermis (also includes connective tissues)
- Sub-cutaneous (Hypo-dermis)

Dermis
- Sebaceous Gland (secrets oil - sebum)
- nerve endings
- Blood capillaries
- Hair follicle
- Adipose Tissue
- artery
- vein
- capillary bed

Sebaceous Gland
- Erector muscle (for making hair stand "on end")
- Free nerve endings

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Physiological Factors

Physiological factors that influence the rate of drug delivery include:

Skin age
Body Site
Ethnicity
Other Factors

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Other Factors

Hydration

Skin water content ~15-20% of tissue dry weight

↑ water content with occlusion

In stratum corneum 25-35% of water is ‘bound’ within this layer

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Other Factors

Hydrophilic

Hydrophilic

Hydrophilic

Liphophilic

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Factors for Drug Absorption

Physico-Chemical Properties

Solubility

Lipophilic agents penetrate well across the stratum corneum

Hydrophilic agents absorb better in aqueous layers of the epidermis

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Factors for Drug Absorption

Skin Characteristics
Physico-Chemical Properties
Chemical Penetration Enhancers
Vehicle Base

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Chemical Penetration Enhancers

Act reversibly
Potencies appear to be drug specific
Work well with co-solvents
Concentration dependent effect
Potential mechanism of action of enhancers are varied

Williams A. Transdermal and topical drug delivery: from theory to clinical practice, 2003
Finding a Suitable Vehicle

Passive diffusion into superficial epidermis sufficient for skin penetration

Drug/vehicle must maintain affinity for aqueous & lipid environments to absorb effectively into systemic circulation

G Harochaw, Personal communication
Vehicles Used

PLO – **Pluronic Lecithin Organogel**

Pluronic → hydrophilic phase
Lecithin Isopropyl Palmitate → lipophilic phase

Wiler’s PCCA
Vehicles Used

Gold Standard

PLO
  Template Vehicle
  Process Benefits
  Structural/Physical Stability
  Topical Delivery Potential
  Safety

Vehicles Used

Change PLO → Lipoderm
  - Less chance of rash vs PLO
  - Products don’t separate as easily
  - Only compounding pharmacies can make

Hydro-Alcoholic Gels
  - Disappears into the skin much faster than PLO
  - Agents used in gel must dissolve completely in water or alcohol (Not with PLO)
Vehicles To Be Used

Penetration rates:

- Pentravan, VanPen, PLO → 5-20mm
- PCCA Gel 2058 → 1-3mm
- PCCA Gel 4038 → 10-20mm
- PCCA Gel 6633 → +30mm
- Speed Gel → up to 50mm

Wiler’s PCCA
Pain Physiology
Pain PATHWAY

Endorphins
Enkephalins

Pain perception

Histamine
Leukotrienes
Bradykinin
Prostaglandins

Descending

Substance P
Aspartate
Glutamate
Nitric Oxide

Spinal cord
Inhibition of Neurotransmitters

Voltage-Gated Na\(^+\) Channel Antagonist
\(\alpha_2\)-Adrenoceptor Agonist
NE Reuptake Inhibitor
Glutamate Antagonist
NMDA Antagonist
Voltage-Gated Na⁺ Channel Antagonist

Lidocaine

Alters depolarization in neurons by blocking the voltage gated Na⁺ channels in the cell membrane

Inhibits depolarization = NO action potential = anesthetic effects

Katzung B Basic & Clinical Pharmacology, 7th ed 1998
α₂-Adrenoceptor Agonist

Clonidine

Specificity towards presynaptic α2 receptors
α2 receptors located in peripheral and central terminals

↓ Ca²⁺ levels = ↓ neurotransmission

Lipophilic

Katzung B Basic & Clinical Pharmacology, 7th ed 1998
NE Reuptake Inhibitor

Tricyclic Antidepressants

Amitriptyline

Inhibition of nociceptive transmission via ↑ in synaptic NE, 5-HT₃

Blockade of α-adrenergic receptors

?Anticholinergic effects

Extremely lipophilic

Katzung B Basic & Clinical Pharmacology, 7th ed 1998
Glutamate Antagonist

**Gabapentin**

Analog of gamma-aminobutyric acid

Works via binding to the α2δ subunit of the voltage-gated N-type Ca^{++} ion channel

Modulates the Ca^{++} channel & ↓ Ca^{++} influx

↓ presynaptic glutamate release


Taylor CP. *CNS Drug Rev* 2004;10:183-188
NMDA Antagonist

Ketamine
N-methyl-D-aspartate antagonist
Ionotropic receptor for glutamate
Both ligand-gated & voltage-gated
Activation results in opening of an ion channel
Calcium flux may be critical for synaptic plasticity

Katzung B Basic & Clinical Pharmacology, 7th ed 1998
Presynaptic Neuron

Glu  Glu  Glu
V-G Ca²⁺

Ca²⁺  Ca²⁺  Ca²⁺  Ca²⁺

GABA

V-G Ca²⁺

Ketamine

GABA

Glu  Glu

AMP  AMP  AMPA  AMPA

Postsynaptic Neuron

DEPOLARIZATION

Cytoplasm

AM  PA
NMDA  NM

V-G Na⁺  V-G Na⁺

α²  α²
General Formulation “Rules”

Select a Drug
Estimate Drug Penetration
Select a Vehicle
?Role of Chemical Penetration Enhancer
Be Realistic
### Table 1. Algorithm for the Treatment of Chronic Neuropathic Pain.¹

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug or Drug Class</th>
<th>Route of Administration</th>
<th>Topical</th>
<th>Oral</th>
<th>Rectal</th>
<th>Nasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA antagonists</td>
<td>Ketamine</td>
<td>5% to 10%</td>
<td>Reported</td>
<td>Reported</td>
<td>Reported at 5% and 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amantadine</td>
<td>5% to 10%</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td>5% to 10%</td>
<td>Reported</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Orphenadrine</td>
<td>5% to 10%</td>
<td>100 mg</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glutamate antagonist</td>
<td>Gabapentin (?)</td>
<td>6%</td>
<td>300 mg to 3 g daily, divided</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>α-2 agonist</td>
<td>Clonidine</td>
<td>0.1% to 0.2%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sympatholytic</td>
<td>Amitriptyline</td>
<td>2% to 5%</td>
<td>Reported</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;β&lt;/sub&gt; agonist</td>
<td>Baclofen</td>
<td>2% to 5%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mu agonists</td>
<td>Loperamide</td>
<td>5% to 10%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TNF-1α antagonist</td>
<td>Pentoxifylline</td>
<td>5% to 10%</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Skeletal-muscle relaxer</td>
<td>Guaifenesin</td>
<td>10%</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L-Type calcium blocker</td>
<td>Nifedipine</td>
<td>2% to 16% depending on the size of the treated area</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NMDA sodium channel blocker</td>
<td>Carbamazepine (?)</td>
<td>2% to 5%</td>
<td>Reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Lidocaine</td>
<td>2% to 10%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Tetracaine</td>
<td>2% to 10%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine</td>
<td>0.5% to .75%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NMDA = N-methyl-D-aspartate

? = Drug or drug class undetermined

GABA<sub>β</sub> = γ-aminobutyric acid<sub>β</sub>

TNF-1α = Tumor necrosis factor-1α

Historically, treatment with ketamine, gabapentin, and clonidine is initiated as described above. Then one or more of the other drugs is added.

Jones M IJPC 2002; 6:4-6

Modified December 2001.
Transdermal Delivery

Drugs listed in percentages

1% Solution = 1000mg/100ml
(10mg/ml)

Morphine 1% solution
Ketamine 5% in gel
### Transdermal Delivery: Meds

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>1-5%</td>
<td>NE reuptake inhibitor</td>
</tr>
<tr>
<td>Baclofen</td>
<td>2-5%</td>
<td>$\text{GABA}_\beta$ agonist</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.025-0.1%</td>
<td>Substance P blockade</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1-0.3%</td>
<td>$\alpha_2$-Adrenoceptor agonist</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2-10%</td>
<td>Cyclo-oxygenase inhibitor</td>
</tr>
</tbody>
</table>
Transdermal Delivery: Meds

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>5-10%</td>
<td>Glutamate antagonist</td>
</tr>
<tr>
<td>Ketamine</td>
<td>5-15%</td>
<td>NMDA-receptor antagonist</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>5-10%</td>
<td>Propionic acid NSAID</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2-10%</td>
<td>Anaesthetic</td>
</tr>
<tr>
<td>Loperamide</td>
<td>5-10%</td>
<td>Mu (µ) agonist</td>
</tr>
</tbody>
</table>
Transdermal Neuropathics

Four way X-over study, 20 pts c neuropathic pain
2 d blinded trial
Amitriptyline(A) 1% vs ketamine(K) 0.5% vs
A 1% + K 0.5% vs PLO gel
No relief for any patient
11 pts in open label cohort
Topical A 1% + K 0.5% gel applied QID x 7 d

Significant pain response noted with use of combination gel
Rash, burning at site in 2 pts
No significant systemic absorption of any of the medications
Topical meds need time to work

Transdermal Neuropathics

Retrospective, orofacial pain pts (n=39)
Systemic Rx, topical, both
Topical (apply 4-6 x daily) contains:
  carbamazepine 4%  lidocaine 1%
  ketoprofen 4%  ketamine 4%
  gabapentin 4%
Pain measured baseline and at clinic visits
VAS, 30% reduction = good result

Heir G et al. OOOOE 2008:105:446-9
Best relief with combined therapies
Shortest time to relief c topicals
AEs? Standard Rx? doses?
Good start for line of research
Prospective trials needed

Heir G et al. OOOOE 2008:105:446-9
Pain & Symptom Management Clinic

Multidisciplinary assessment/treatment of pts with symptoms related to cancer or its treatment(s)

Provide consultation, follow-up/evaluation of interventions

Symptoms suitable for clinic

Referral from several sources
Pharmacy Collaboration

Improved patient outcomes through:

- Education of patients/family/allied healthcare members
- Monitoring of adverse effects
- Drug information/counseling
- Medication management
Date: ____________________________
Patient Name ____________________________
Address: ______________________________________
Date of Birth: ____________________________
PHIN: ______________________________________

Base: 
- □ Lipoderm 
- □ PLO 
- □ Speed Gel 
- □ Other (specify) _________________________

Check the Ingredient & Strength: 

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
<th>30%</th>
<th>(requires a duplicate Rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>___</td>
<td>___</td>
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<tr>
<td>Loperamide</td>
<td>___</td>
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<td>___</td>
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<td></td>
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<tr>
<td>Ketoprofen</td>
<td>___</td>
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<tr>
<td>Diclofenac</td>
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Additional Ingredients: _________________________ %

Sig: Apply _____mL to affected area(s) ____________ (frequency) ________________________.

Mitte: _______ mL Refill x _______

Physician Name (Print): ____________________________
Address: ______________________________________
Phone: ______________________________________
Signature: ____________________________________

G Harochaw  
D Wong  
P Daeninck
Transdermal Neuropathics

1st combination we use:
  Ketamine 5-15%   Gabapentin 6-8%
  Lidocaine 2-6%
1st time use success rate ~ 30%
Adjust %, add others, add DMSO
Success after “fine tuning” gel ~ 70%

G Harochaw, Personal Communication
Clinical Challenges

Follow-up with patients after initial use:
If able to contact, can adjust topical to work 70% of time
Incorrect application (regardless of counselling)
  too small an amount
  applying to wrong area
  rubbing too aggressively → creating pain
Poor compound selection
Communication/compliance issues
  physicians
  patients

G Harochaw, Personal Communication
Results from Clinic

Referrals to P & S clinic

13 patients
- 8 post therapy neuropathy (CT, RT, surgery)
- 4 due to disease (breast ca)
- 1 other (Zoster infection)

Ketamine/lidocaine common to all
Other Rx: ketoprofen, gabapentin, loperamide
PLO or lipoderm
TID to QID application
Results from Clinic

Complete information in 11 pts
All had some benefit (↓VAS)
1 stopped: worsening pain
Adjustments often improved pain control
5 concomitant Rx (opioids, pregabalin)
Compliance may be a problem
A/E: nil
Pts complaints: cost, greasy feeling, inconv.
Results from Clinic

66 yo male, Stage III Colon, FOLFOX x 12
Hands/feet neuropathy (8-9/10 baseline)
Several oral drugs (opioids, TCA, anti-epileptics)
Methadone (6/10 best result)
PLO gel with ketamine 5%, lidocaine 2%,
   gabapentin 4%, apply TID
Improved 4/10, ↑ gabapentin to 6%
Present pain rated as 2/10
Where are we going?

Which patients benefit most?

Treatment algorithm?

  which drugs?
  which carriers?
  condition specific?
  topical alone or with systemic therapy?

Formalize a protocol

  meds, follow-up, timing

? Clinical trial
Synthetic cannabinoids
20-30 x more potent than Δ⁹-THC
Benefits seen in emesis, glaucoma, pain
Fig. 2. Mean (±S.D.) cumulative amount of WIN 55,212-2 permeated across the human skin into 0.5% Brij 98 and 4% BSA receiver solutions.

Fig. 3. Mean (±S.D.) cumulative amount of CP 55,940 permeated across the human skin into 0.5% Brij 98 and 4% BSA receiver solutions.
Summary

Pts with advanced diseases may require alternative routes for Rx administration.
Topical compounds gaining popularity.
Evidence for opioids, topicals emerging.
Clinical trial support lacking.
Collaboration with pharmacy invaluable.
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